Molecular basis of human ES cell neurovascular differentiation and co-patterning

Grant Award Details

Molecular basis of human ES cell neurovascular differentiation and co-patterning

Grant Type: Basic Biology III

Grant Number: RB3-02098

Project Objective: Understanding how autonomic neurons emerge from their precursors and whether aligning with blood vessels helps their differentiation is critical for the development of regenerative therapies and the production of organs with functional blood vessel networks equipped with autonomic control. The overall goal of this proposal is to investigate how vascular alignment functions as a driver of autonomic neuronal fate.

Investigator:

Name:	David Cheresh
Institution:	University of California, San Diego
Type:	PI

Human Stem Cell Use: Embryonic Stem Cell

Award Value: $1,359,996

Status: Closed

Progress Reports

Reporting Period: Year 1

View Report

Reporting Period: Year 2

View Report

Reporting Period: Year 3

View Report

Grant Application Details

Application Title: Molecular basis of human ES cell neurovascular differentiation and co-patterning

Public Abstract: During human development, autonomic neurons align with and pattern alongside blood vessels. This patterning allows the autonomic nervous system to control the vascular function a phenomenon that is very useful during situations such as "fight or flight" responses where the blood vessels need to respond rapidly and involuntarily to stimuli. Since the alignment of blood vessels with autonomic neurons occurs during embryogenesis, human embryonic stem cells provide a system in which we can observe and understand how neurons and blood vessels differentiate and co-align to form a neurovascular unit.

We have developed a human embryonic stem cell differentiation model where we are able to visualize the early stages of human blood vessel and neuronal development and their co-alignment and patterning in real time over a period of three weeks. Using this model, we have identified a cell-adhesion protein T-Cadherin, present on both the blood vessels and neurons, which may act as the "molecular velcro" in attaching neuronal cells to the blood vessel networks. We have also identified small RNA molecules termed microRNAs that may regulate T-Cadherin protein expression during this process. In this context, we propose that the regulation of T-Cadherin expression by specific microRNAs leads to the differentiation of autonomic neurons and their co-patterning with the network of blood vessels. We will test this hypothesis in three distinct aims:

1. Is T-Cadherin expression necessary and sufficient to drive the formation of the neurovascular unit?

2. Does microRNA regulation of T-Cadherin expression affect neurovascular co-patterning?

3. Can we manipulate T-Cadherin expression to generate viable autonomic neurons from hES cells for possible therapeutic use?

A number of human disorders result from abnormal patterning or development of autonomic neurons. For example, Hirschsprung's disease in infants results from improper nerve development in the gut, leading to chronic bowel obstruction that necessitates immediate surgical intervention. Understanding how autonomic neurons emerge from their precursors and whether aligning with blood vessels are required for their differentiation is critical to develop regenerative therapies. Furthermore, understanding how proteins like T-Cadherin regulate fundamental interactions of different cell types such as blood vessels and neurons offers insights into organ development and tissue engineering.

Statement of Benefit to California: During human development, specific types of neuronal cells termed 'autonomic neurons' align and pattern along with blood vessels. Autonomic neurons are part of the peripheral nervous system that controls many involuntary functions, including heart rate and blood pressure. Lack of proper autonomic neuronal development or degeneration of existing autonomic neurons can lead to human diseases such as Hirschsprung's disorder, in which improper development of autonomic neurons in the gut results in bowel obstruction. This research proposal aims to understand how blood vessels help the differentiation of autonomic neurons. To this end, our studies will employ a novel human embryonic stem cell differentiation model in which both neurons and blood vessels develop in the context of all three germ layers. The understanding gained from our proposed studies will broadly benefit several categories of patients in California, including those with autonomic nervous system disorders. Furthermore, gaining fundamental insight into neurovascular patterning using this model system will facilitate development of functional blood vessels with proper autonomic innervation for tissue engineering applications that will benefit large numbers of patients in California.

This project will also serve to accelerate innovation of human ES cell and microRNA therapeutics in California, to train more people in California to work on this cutting-edge technology, and to establish the foundation for the design of regenerative therapies for neurovascular disorders that will benefit a significant number of citizens of California.